PATENT
Attorney Docket No. 401371/NIH

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

BURKE, Jr., et al.

Application No. Unassigned

Filed: Herewith

For: PHENYLALANINE DERIVATIVES

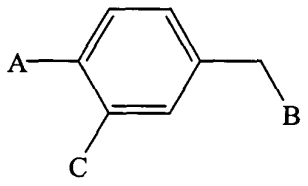
Art Unit: Unassigned

Examiner: Unassigned

AMENDMENTS TO CLAIMS MADE VIA PRELIMINARY AMENDMENT

Amendments to existing claims:

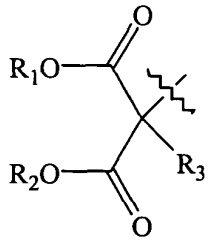
1. (Amended) A compound of formula I:



(I),

wherein:

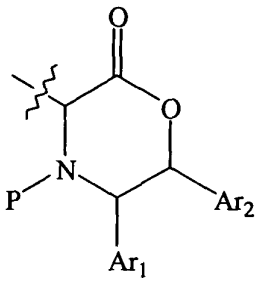
A is carboxyl, carboxyalkyl, dicarboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, dialkoxycarbonylalkyl, or a malonyl group of formula II:



(II),

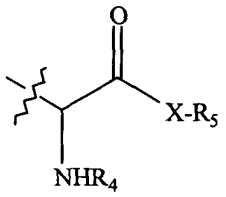
wherein R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, alkylaryl, and heteroaryl; and R_3 is selected from the group consisting of hydrogen, halo, hydroxy, amino, alkyl, aryl, and alkoxy;

B has the formula III:



(III),

wherein P is an amine ~~protective~~ protecting group; and Ar_1 and Ar_2 are aryl groups; or the formula IV:



(IV),

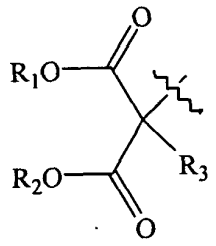
wherein X is NH or O; R_4 is hydrogen, alkyl, aryl, alkylaryl, arylalkyl, or an amine protective group; and R_5 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, alkylaryl, and heteroaryl; and

C is selected from the group consisting of hydrogen, hydroxyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkoxycarbonyl, and alkoxycarbonyl alkyl;

wherein said aryl, heteroaryl, and the aryl portion of said arylalkyl and alkylaryl may be unsubstituted or substituted with a substituent selected from the group consisting of alkyl, hydroxy, halo, keto, amino, and alkoxy; with the provisos that (i) R_5 is not hydrogen when A is carboxyl or carboxyalkyl, C is hydrogen, B has the formula IV wherein R_4 is hydrogen or alkylcarbonyl, and X is NH; and (ii) R_5 is not hydrogen or alkyl when A is carboxyl or carboxyalkyl, C is hydrogen or hydroxy, B has the formula IV wherein R_4 is hydrogen or alkylcarbonyl, and X is O.

2. (Amended) The compound of claim 1, wherein:

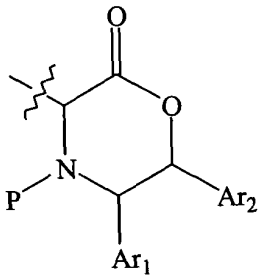
A is carboxyl, carboxyl C_1-C_6 alkyl, dicarboxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonyl C_1-C_6 alkyl, C_1-C_6 dialkoxycarbonyl C_1-C_6 alkyl, or a malonyl group of formula II:



(II),

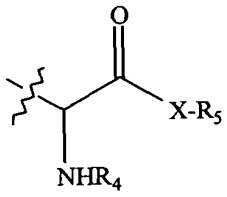
wherein R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkylaryl, and heteroaryl; and R_3 is selected from the group consisting of hydrogen, halo, hydroxy, amino, C_1-C_6 alkyl, aryl, and C_1-C_6 alkoxy;

B has the formula III:



(III),

wherein P is an amine ~~protective~~ protecting group; and Ar_1 and Ar_2 are aryl groups; or B has the formula IV:

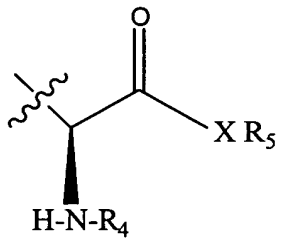


(IV),

wherein X is NH or O; R_4 is hydrogen, C_1-C_6 alkyl, aryl, C_1-C_6 alkylaryl, aryl C_1-C_6 alkyl, or an amine ~~protective~~ protecting group; and R_5 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkylaryl, and heteroaryl; and

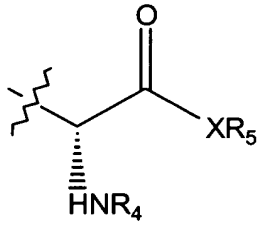
C is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyl, and C_1-C_6 alkoxycarbonyl C_1-C_6 alkyl; wherein said aryl, heteroaryl, and the aryl portion of said arylalkyl and alkylaryl may be unsubstituted or substituted with a substituent selected from the group consisting of C_1-C_6 alkyl, hydroxy, halo, keto, amino, and C_1-C_6 alkoxy.

4. (Amended) The compound of claim 3, wherein B has the formula:



wherein X is NH or O; R_4 is hydrogen, C_1-C_6 alkyl, aryl, C_1-C_6 alkylaryl, aryl C_1-C_6 alkyl, or an amine ~~protective~~ protecting group; and R_5 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkylaryl, and heteroaryl.

5. (Amended) The compound of claim 3, wherein B has the formula:

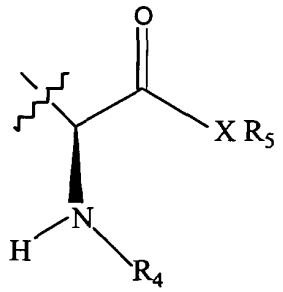


wherein X is NH or O; R_4 is hydrogen, C_1-C_6 alkyl, aryl, C_1-C_6 alkylaryl, aryl C_1-C_6 alkyl, or an amine ~~protective~~ protecting group; and R_5 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkylaryl, and heteroaryl.

6. (Amended) The compound of claim ~~4 or 5~~, wherein X is O.

9. (Amended) The compound of claim 8, wherein ~~acid~~ the amine protecting group is selected from the group consisting of fluorenylmethoxycarbonyl, tert-butoxycarbonyl, carbobenzoxy, and carbamoyl.

24. (Amended) The compound of claim ~~1 or 2~~, wherein R_1 and R_2 are tert-butyl ~~and~~, R_3 is hydrogen, and B has the formula



wherein X is O, R_4 is fluorenylmethoxycarbonyl, and R_5 is hydrogen.

34. (Amended) A conjugate comprising a conjugant covalently linked to a compound of ~~any of claims 1-25~~ claim 1.

44. (Amended) The compound of ~~any of claims 41-43~~ claim 41, wherein E is hydrogen.

46. (Amended) The compound of ~~any of claim 41-45~~ claim 41, wherein R_3, R_4, R_5, and R_6 are hydrogen.

48. (Amended) The compound of ~~any of claims 38-47~~ claim 38, wherein W is selected from the group consisting of C_1-C_6 alkylcarbonyl, oxalyl, C_1-C_6 alkylaminooxalyl, arylaminooxalyl, aryl C_1-C_6 alkylaminooxalyl, C_1-C_6 alkoxyoxalyl, carboxy C_1-C_6 alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C_1-C_6 alkyl carbonyl, aryl C_1-C_6 alkyl heterocyclyl C_1-C_6 alkyl carbonyl, aryloxycarbonyl, and aryl C_1-C_6 alkoxycarbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C_1-

C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S.

66. (Amended) The compound of ~~any of claims 38-65~~ claim 38, wherein Z is aryl C_1-C_6 alkylamino.

71. (Amended) The compound of ~~any of claims 38-65~~ claim 38, wherein Z is aryl heterocyclyl C_1-C_6 alkylamino.

77. (Amended) The compound of ~~any of claims 38-76~~ claim 38, wherein said amino acid is selected from the group consisting of glycine, alanine, valine, norvaline, leucine, iso-leucine, norleucine, α-amino n-decanoic acid, serine, homoserine, threonine, methionine, cysteine, S-acetylaminomethyl-cysteine, proline, trans-3- and trans-4-hydroxyproline, phenylalanine, tyrosine, 4-aminophenylalanine, 4- nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenylserine β-hydroxyphenylalanine, phenylglycine, α-naphthylalanine, cyclohexylalanine, cyclohexylglycine, tryptophan, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aspartic acid, asparagine, aminomalonic acid, aminomalonic acid monoamide, glutamic acid, glutamine, histidine, arginine, lysine, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine, α-aminocyclopentane carboxylic acid, α-aminocyclohexane carboxylic acid, α-aminocycloheptane carboxylic acid, α-(2-amino-2-norbornane)-carboxylic acid, α,γ-diaminobutyric acid ~~and~~, α,β-diaminopropionic acid, homophenylalanine, and α-tert-butylglycine.

84. (Amended) A composition comprising a pharmacologically acceptable carrier and a compound of ~~any of claims 38-83~~ claim 38.

85. (Amended) A method for inhibiting an SH2 domain from binding with a phosphoprotein comprising contacting an SH2 domain with a compound of ~~any of claims 34-83~~ claim 38.

90. (Amended) A method for inhibiting SH2 domain binding comprising exposing a material containing an SH2 domain to a compound of ~~any of claims 34-83~~ claim 38.

91. (Amended) A method for determining the presence of an SH2 domain in a material comprising:

(a) exposing a sample of said material to a SH2 binding compound and obtaining a first binding result;

(b) exposing another sample of said material to a compound of ~~any of claims 34-83~~ claim 38 and obtaining a second binding result; and

(c) comparing the first and second binding results to determine whether an SH2 domain is present in the material.

92. (Amended) A method of preventing or treating a disease, state, or condition in a mammal comprising administering a compound of ~~any of claims 34-83~~ claim 38.

106. (Amended) A method of enhancing the therapeutic effect of a treatment rendered to a mammal that has been afflicted with a disease, state, or condition, comprising administering to the mammal a compound of ~~any of claims 38-83~~ claim 38 in conjunction with the treatment.

112. (Amended) A method of inhibiting the MAP kinase activity in a mammal comprising administering to the mammal a compound of ~~any of claims 34-83~~ claim 38.

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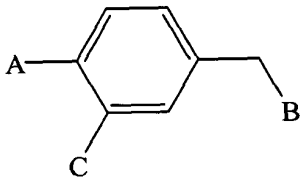
PENDING CLAIMS AFTER ENTRY OF PRELIMINARY AMENDMENT

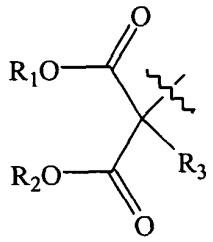
1. A compound of formula I:



(I),

wherein:

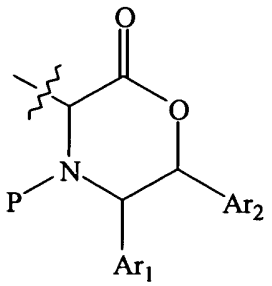
A is carboxyl, carboxyalkyl, dicarboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, dialkoxycarbonylalkyl, or a malonyl group of formula II:



(II),

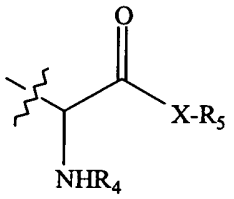
wherein R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, alkylaryl, and heteroaryl; and R_3 is selected from the group consisting of hydrogen, halo, hydroxy, amino, alkyl, aryl, and alkoxy;

B has the formula III:



(III),

wherein P is an amine protecting group; and Ar_1 and Ar_2 are aryl groups; or the formula IV:



(IV),

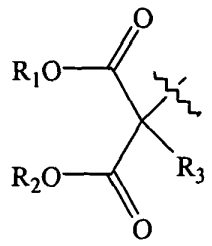
wherein X is NH or O; R_4 is hydrogen, alkyl, aryl, alkylaryl, arylalkyl, or an amine protective group; and R_5 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, alkylaryl, and heteroaryl; and

C is selected from the group consisting of hydrogen, hydroxyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkoxycarbonyl, and alkoxycarbonyl alkyl;

wherein said aryl, heteroaryl, and the aryl portion of said arylalkyl and alkylaryl may be unsubstituted or substituted with a substituent selected from the group consisting of alkyl, hydroxy, halo, keto, amino, and alkoxy; with the provisos that (i) R_5 is not hydrogen when A is carboxyl or carboxyalkyl, C is hydrogen, B has the formula IV wherein R_4 is hydrogen or alkylcarbonyl, and X is NH; and (ii) R_5 is not hydrogen or alkyl when A is carboxyl or carboxyalkyl, C is hydrogen or hydroxy, B has the formula IV wherein R_4 is hydrogen or alkylcarbonyl, and X is O.

2. The compound of claim 1, wherein:

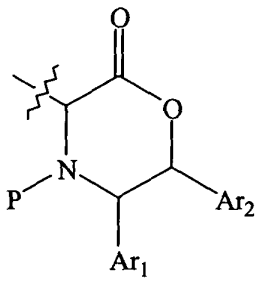
A is carboxyl, carboxyl C_1-C_6 alkyl, dicarboxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonyl C_1-C_6 alkyl, C_1-C_6 dialkoxycarbonyl C_1-C_6 alkyl, or a malonyl group of formula II:



(II),

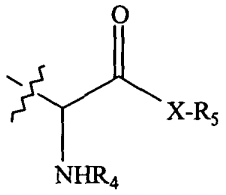
wherein R_1 and R_2 may be the same or different and are selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkylaryl, and heteroaryl; and R_3 is selected from the group consisting of hydrogen, halo, hydroxy, amino, C_1-C_6 alkyl, aryl, and C_1-C_6 alkoxy;

B has the formula III:



(III),

wherein P is an amine protecting group; and Ar_1 and Ar_2 are aryl groups; or B has the formula IV:



(IV),

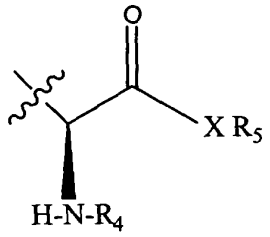
wherein X is NH or O; R_4 is hydrogen, C_1-C_6 alkyl, aryl, C_1-C_6 alkylaryl, aryl C_1-C_6 alkyl, or an amine protecting group; and R_5 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkylaryl, and heteroaryl; and

C is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyl, and C_1-C_6 alkoxycarbonyl C_1-

C_6 alkyl; wherein said aryl, heteroaryl, and the aryl portion of said arylalkyl and alkylaryl may be unsubstituted or substituted with a substituent selected from the group consisting of C_1-C_6 alkyl, hydroxy, halo, keto, amino, and C_1-C_6 alkoxy.

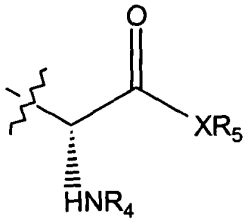
3. The compound of claim 2, wherein B has the formula IV.

4. The compound of claim 3, wherein B has the formula:



wherein X is NH or O; R_4 is hydrogen, C_1-C_6 alkyl, aryl, C_1-C_6 alkylaryl, aryl C_1-C_6 alkyl, or an amine protecting group; and R_5 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkylaryl, and heteroaryl.

5. The compound of claim 3, wherein B has the formula:



wherein X is NH or O; R_4 is hydrogen, C_1-C_6 alkyl, aryl, C_1-C_6 alkylaryl, aryl C_1-C_6 alkyl, or an amine protecting group; and R_5 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkylaryl, and heteroaryl.

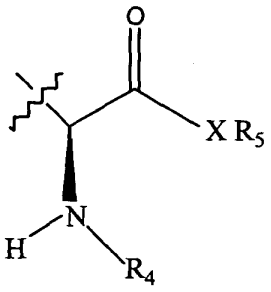
6. The compound of claim 4, wherein X is O.

7. The compound of claim 6, wherein R_4 is hydrogen.

8. The compound of claim 6, wherein R_4 is an amine protecting group.

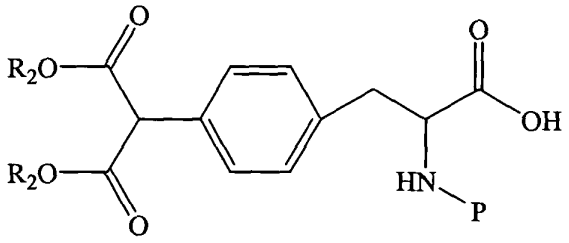
9. The compound of claim 8, wherein the amine protecting group is selected from the group consisting of fluorenylmethoxycarbonyl, tert-butoxycarbonyl, carbobenzoxy, and carbamoyl.

24. The compound of claim 1, wherein R_1 and R_2 are tert-butyl, R_3 is hydrogen, and B has the formula



wherein X is O, R_4 is fluorenylmethoxycarbonyl, and R_5 is hydrogen.

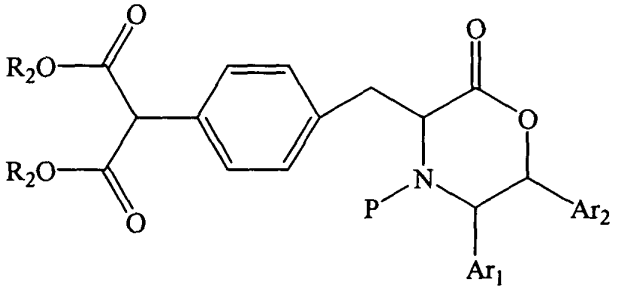
26. A process for preparing a compound of formula VIII:



(VIII),

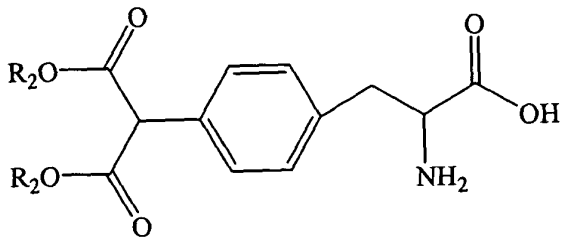
wherein R_2 is alkyl and P is an amine protecting group; the process comprising:

(a) reducing the compound of formula



(VII),

to obtain a compound of formula IX:

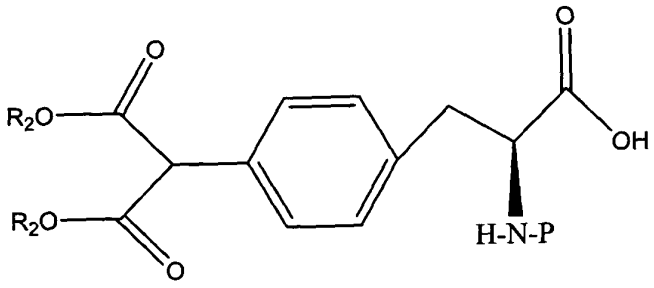


(IX);

and

(b) reacting the compound of formula IX with an amine protecting agent to obtain the compound of formula VIII.

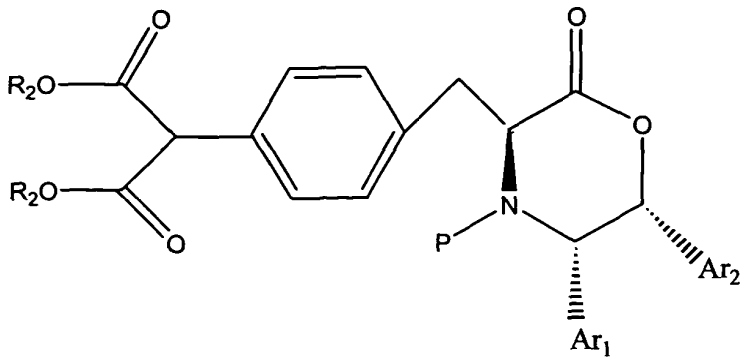
29. A process for preparing a compound of formula VIIIa:



(VIIIa)

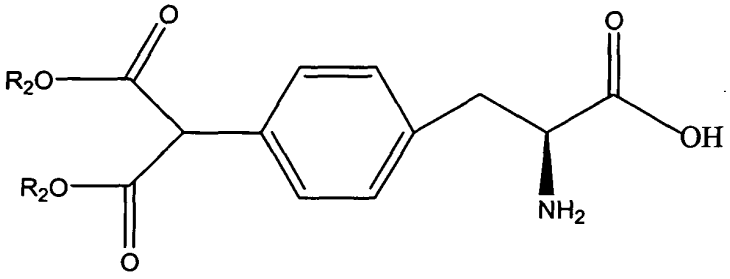
wherein R_2 is alkyl and P is an amine protecting group; the process comprising:

(a) reducing a compound of formula VII



(VIIa)

to obtain a compound of formula IXa:

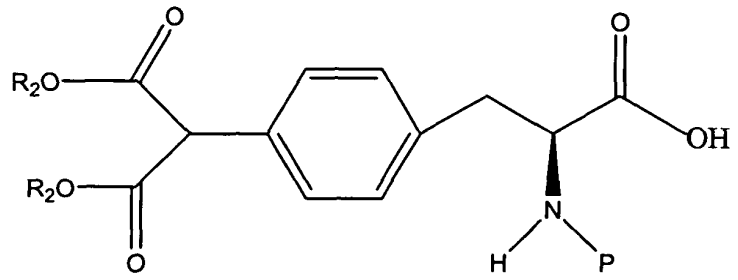


(IXa);

and

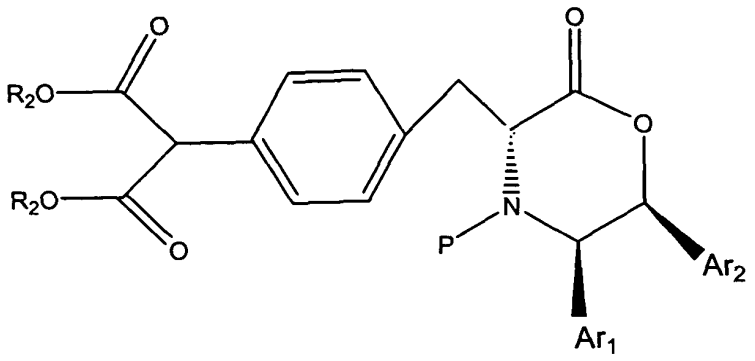
(b) reacting the compound of formula IXa with an amine protecting agent to obtain the compound of formula VIII.

30. A process for preparing a compound of the formula:

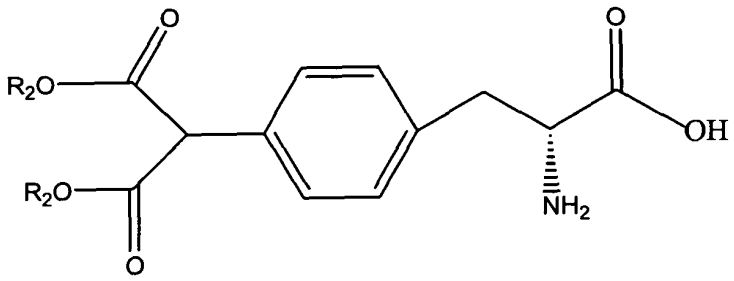


wherein R_2 is alkyl and P is an amine protecting group; the process comprising:

(a) reducing a compound of formula:



to obtain a compound of formula IXb:



(IXb);

and (b) reacting the compound of formula IXa with an amine protecting agent to obtain the compound of formula VIII.

34. A conjugate comprising a conjugant covalently linked to a compound of claim 1.

38. A compound of the formula:

$$W\text{-}Y\text{-}(AA)_n\text{-}Z$$

wherein n is 0 to 15;

Y is a phenylalanyl radical having a phenyl ring, an amine end, and a carboxyl end, the phenyl ring having one or more substituents selected from the group consisting of hydroxyl, carboxyl, formyl, carboxyalkyl, carboxyalkyloxy, dicarboxyalkyl, dicarboxyalkyloxy, dicarboxyhaloalkyl, dicarboxyhaloalkyloxy, and phosphonoalkyl, phosphonohaloalkyl, wherein the alkyl portion of the substituents may be unsubstituted or

substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, alkyl, alkoxy, and keto;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of alkylcarbonyl, oxalyl, alkylaminooxalyl, arylaminooxalyl, arylalkylaminooxalyl, alkoxyoxalyl, carboxyalkyl carbonyl, heterocyclyl carbonyl, heterocyclylalkyl carbonyl, arylalkyl heterocyclylalkyl carbonyl, aryloxycarbonyl, and arylalkoxycarbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, alkyl, alkoxy, and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and

Z is an arylalkylamino or arylheterocyclyl alkylamino;

or a salt thereof;

with the proviso that W is not arylalkylamino when the phenyl ring of phenylalanyl contains a phosphonoalkyl or phosphonohaloalkyl substituent at a position para to the alkylamido group and the ortho and meta positions are unsubstituted.

39. The compound of claim 38, wherein n is 0 to 15;

Y is a phenylalanyl radical having a phenyl ring, an amine end, and a carboxyl end, the phenyl ring having one or more substituents selected from the group consisting of hydroxyl, carboxyl, formyl, carboxy C_1-C_6 alkyl, carboxy C_1-C_6 alkyloxy, dicarboxy C_1-C_6 alkyl, dicarboxy C_1-C_6 alkyloxy, dicarboxyhalo C_1-C_6 alkyl, dicarboxyhalo C_1-C_6 alkyloxy, and phosphono C_1-C_6 alkyl, phosphonohalo C_1-C_6 alkyl, wherein the alkyl portion of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, and keto;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of C_1-C_6 alkylcarbonyl, oxalyl, C_1-C_6 alkylaminooxalyl, arylaminooxalyl, aryl C_1-C_6 alkylaminooxalyl, C_1-C_6 alkoxyoxalyl, carboxy C_1-C_6 alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C_1-C_6 alkyl carbonyl, aryl C_1-C_6 alkyl heterocyclyl C_1-C_6 alkyl carbonyl, aryloxycarbonyl, and aryl C_1-C_6 alkoxycarbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy,

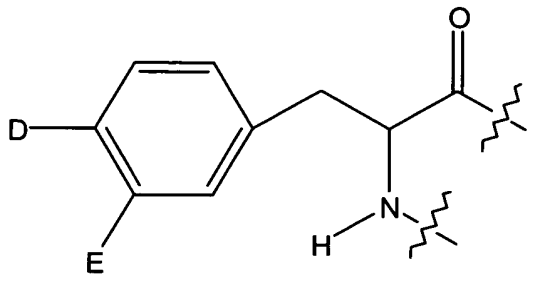
and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and

Z is an aryl C_1-C_6 alkylamino or arylheterocyclyl C_1-C_6 alkylamino;

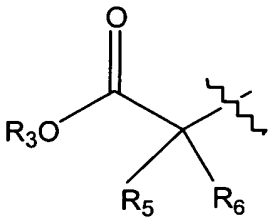
or a salt thereof.

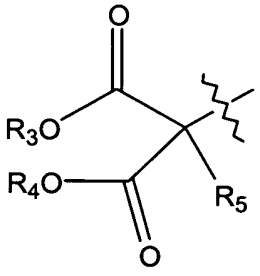
40. The compound of claim 39, wherein Y is of the formula XI:

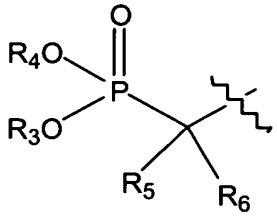


(XI)

wherein D has the formula XII, XIII, or XIV:







(XII) (XIII) (XIV)

wherein R_3 and R_4 may be the same or different and are selected from the group consisting of hydrogen, C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, C_1-C_6 alkaryl, and heteroaryl; and R_5 and R_6 may be the same or different and are selected from the group consisting of hydrogen, halo, hydroxy, amino, and C_1-C_6 alkoxy; and

E is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, carboxyl, and C_1-C_6 alkylcarbonyl C_1-C_6 alkyl.

41. The compound of claim 40, wherein D is of formula XII.

42. The compound of claim 40, wherein D is of formula XIII.

43. The compound of claim 40, wherein D is of formula XIV.

44. The compound of claim 41, wherein E is hydrogen.

45. The compound of claim 41, wherein E is carboxyl.

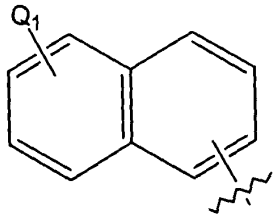
46. The compound of claim 41, wherein R_3, R_4, R_5, and R_6 are hydrogen.

47. The compound of claim 43, wherein R_3 and R_4 are hydrogen.

48. The compound of claim 38, wherein W is selected from the group consisting of C_1-C_6 alkylcarbonyl, oxalyl, C_1-C_6 alkylaminooxalyl, arylaminooxalyl, aryl C_1-C_6 alkylaminooxalyl, C_1-C_6 alkoxyoxalyl, carboxy C_1-C_6 alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C_1-C_6 alkyl carbonyl, aryl C_1-C_6 alkyl heterocyclyl C_1-C_6 alkyl carbonyl, aryloxycarbonyl, and aryl C_1-C_6 alkoxycarbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S.

66. The compound of claim 38, wherein Z is aryl C_1-C_6 alkylamino.

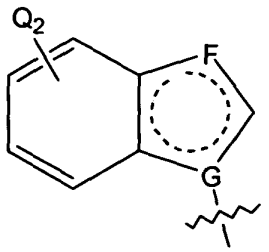
67. The compound of claim 66, wherein the aryl portion of Z has the formula:



wherein Q_1 is hydrogen or a substituent selected from the group consisting of hydroxyl, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and C_1-C_6 acylamino.

71. The compound of claim 38, wherein Z is aryl heterocyclyl C_1-C_6 alkylamino.

72. The compound of claim 71, wherein the heterocyclyl portion of Z has the formula:



wherein Q_2 is hydrogen or a substituent selected from the group consisting of hydroxyl, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and C_1-C_6 acylamino, and F and G are independently selected from the group consisting of C, N, O, and S.

77. The compound of claim 38, wherein said amino acid is selected from the group consisting of glycine, alanine, valine, norvaline, leucine, iso-leucine, norleucine, α-amino n-decanoic acid, serine, homoserine, threonine, methionine, cysteine, S-acetylaminomethyl-cysteine, proline, trans-3- and trans-4-hydroxyproline, phenylalanine, tyrosine, 4-aminophenylalanine, 4- nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenylserine β-hydroxyphenylalanine, phenylglycine, α-naphthylalanine, cyclohexylalanine, cyclohexylglycine, tryptophan, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aspartic acid, asparagine, aminomalonic acid, aminomalonic acid monoamide, glutamic acid, glutamine, histidine, arginine, lysine, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine, α-aminocyclopentane carboxylic acid, α-aminocyclohexane carboxylic acid, α-aminocycloheptane carboxylic acid, α-(2-amino-2-norbornane)-carboxylic acid, α,γ-diaminobutyric acid, α,β-diaminopropionic acid, homophenylalanine, and α-tert-butylglycine.

84. A composition comprising a pharmacologically acceptable carrier and a compound of claim 38.

85. A method for inhibiting an SH2 domain from binding with a phosphoprotein comprising contacting an SH2 domain with a compound of claim 38.

90. A method for inhibiting SH2 domain binding comprising exposing a material containing an SH2 domain to a compound of claim 38.

91. A method for determining the presence of an SH2 domain in a material comprising:
(a) exposing a sample of said material to a SH2 binding compound and obtaining a first binding result;
(b) exposing another sample of said material to a compound of claim 38 and obtaining a second binding result; and
(c) comparing the first and second binding results to determine whether an SH2 domain is present in the material.

92. A method of preventing or treating a disease, state, or condition in a mammal comprising administering a compound of claim 38.

106. A method of enhancing the therapeutic effect of a treatment rendered to a mammal that has been afflicted with a disease, state, or condition, comprising administering to the mammal a compound of claim 38 in conjunction with the treatment.

112. A method of inhibiting the MAP kinase activity in a mammal comprising administering to the mammal a compound of claim 38.

115. A compound of the formula:

$$W\text{-}Y\text{-}(AA)_n\text{-}Z$$

wherein n is 0 to 15;

Y is a phenylalanyl radical having a phenyl ring, an amine end, and a carboxyl end, the phenyl ring having (i) dicarboxy C_1-C_6 alkyl , (ii) hydroxyl and carboxy C_1-C_6 alkyl, (iii) carboxyl and carboxy C_1-C_6 alkyl, or (iv) dicarboxyhalo C_1-C_6 alkyl, or dicarboxyhalo C_1-C_6 alkyloxy; or an ester of (i), (ii), (iii), or (iv); wherein the alkyl portion of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, aminoalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, and keto;

W is a moiety attached to the nitrogen of Y and is selected from the group consisting of C_1-C_6 alkylcarbonyl, oxalyl, C_1-C_6 alkylaminooxalyl, arylaminooxalyl, aryl C_1-C_6 alkylaminooxalyl, C_1-C_6 alkoxyoxalyl, carboxy C_1-C_6 alkyl carbonyl, heterocyclyl carbonyl, heterocyclyl C_1-C_6 alkyl carbonyl, aryl C_1-C_6 alkyl heterocyclyl C_1-C_6 alkyl carbonyl, aryloxycarbonyl, and aryl C_1-C_6 alkoxycarbonyl, wherein the aryl and alkyl portions of the substituents may be unsubstituted or substituted with a substituent selected from the group consisting of halo, hydroxy, carboxyl, amino, amino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy,

and keto; and the heterocyclyl portion of W contains at least 4 hetero atoms selected from the group consisting of O, N, and S;

AA is an amino acid, the amine end of which is attached to the carboxyl end of Y; and

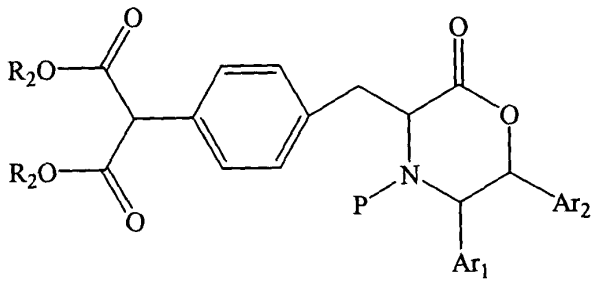
Z is an aryl C_1-C_6 alkylamino or arylheterocyclyl C_1-C_6 alkylamino;

or a salt thereof.

116. A composition comprising a pharmacologically acceptable carrier and a compound of claim 115.

117. A method for inhibiting an SH2 domain from binding with a phosphoprotein comprising contacting an SH2 domain with a compound of claim 115.

118. A process for the preparation of a compound of formula VII:



(VII),

wherein R_2 is alkyl, P is an amine protecting group, and Ar_1 and Ar_2 are aryl; the process comprising:

(a) converting a p-halotoluene to a p-tolyl-malonic acid dialkyl ester by contacting the p-halotoluene with a dialkylmalonate and a cuprous halide;

(b) halogenating the p-tolyl-malonic acid dialkyl ester to obtain a (4-halomethylphenyl)-malonic acid dialkyl ester; and

(c) contacting the (4-halomethylphenyl)-malonic acid ester with a benzyl-6-oxo-2,3-diaryl-4-morpholine to obtain the compound of formula VII.